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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER
SHUKLA, R

ART UNIT	PAPER NUMBER
1632	16

DATE MAILED:

12/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/026,459

Applicant(s)

XU ET AL.

Examiner

Ram Shukla

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-34, 36, 37, and 44-48 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-34, 36, 37, and 44-48 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claims ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some * c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.

18) ☐ Interview Summary (PTO-413) Paper No(s) ____.

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other: ____.

DETAILED ACTION

1. The amendment filed 9-5-00 (paper # 15) has been entered.
2. Claims 35 and 38-43 have been canceled.
3. Amended claims 1, 2, 4-14, 16-17, 19-27, 34, and 36 have been entered.
4. New claims 44-48 have been entered.
5. Claims 1-34, 36, 37 and 44-48 are pending in the instant application.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-34 and 36-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Amended Claims 1 and 36 recite "a proviso that said modified protein does not comprise deletions of amino acids 1 through 378" which indicates exclusion of the deletion of the entire 1-378 amino acid region of an RB protein. However, the specification neither explicitly nor implicitly discloses that the claimed invention excludes deletions of the entire 1-378 amino acids of RB. Rather, the specification discloses that the invention includes deletions of 378 amino acids from the first region of the sequence, which is the N-terminal region (see pages 7 and 8 of the specification).

Accordingly, claims 1-34, 36, and 37 recite a new matter that is not described in the specification.

8. Claims 31-33 remain rejected and newly presented claims 47-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for reasons of record set forth in the previous office action of 3-2-00.

Response to Arguments

9. Applicant's arguments filed 9-5-00 have been fully considered but they are not persuasive. Applicants arguments that applicants specification must be taken as enabling unless there are sufficient reasons to doubt the accuracy of the disclosure and can not be questioned on the unsupported skepticism of the examiner are not persuasive because the issues raised in the previous office action were not skepticism of the examiner, rather they are the issues of unpredictability recognized in the art at the time the invention was made or even after that. It is noted that claims 31-33 have been interpreted to recite gene therapy using the claimed DNA segment. Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise. Therefore, disclosure of expressing claimed DNA in an E.coli cell or any other cell in vitro can not be taken as an enabling disclosure for gene therapy. Applicants have discussed in detail re Brana, 34 USPQ 2D 1437 (Fed. Cir. 1995) and on page 14 give a quote from the case which states that if one has taught some desirable pharmaceutical property in a standard experimental animal it is a useful and significant contribution to art, however, it is not clear as to how this is relevant to the instant application since the specification of the instant application has not taught any pharmaceutical property in an animal. Next the applicants discuss the issue of what is undue experimentation, and that mere unpredictability of result of the experiment is not a consideration, in response it is noted that if the unpredictability issues raised would have been trivial and mere unpredictability of an experiment, the issues raised in the previous office action regarding the method of gene therapy would have been resolved by now, however, even today, three years after the effective filing date of the instant application, these issues make the art of gene therapy unpredictable.

In conclusion, the specification is not enabling for the claimed invention because it does not provide sufficient guidance and working example as to how an artisan of skill would have practiced the claimed invention without undue experimentation.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Amended claims 1, 2, 8, 20, 23, 24, 27, 28-30, 34, 36, and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Fung (US 5,969,120, 10-19-1999, effective filing date, 12-23-1994).

Fung teaches nucleic acids that encode RB mutant proteins wherein amino acids in the region 184-192 were mutated at the 184, 186, 188, 189, and 191. Fung also teaches vectors and host cells expressing said RB mutant proteins. These RB mutants showed growth suppression activity (see column 15, lines 21-25 and table I) in tumor cells.

Accordingly, the invention of claims 1, 2, 8, 20, 23, 24, 27, 28-30, 34, 36, and 37 are anticipated by Fung.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 1, 2, 8, 10, 13, 16, 20-22, 23-30, 34, 36, 37 and 44-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fung in view of Dryja et al (EP 259031, 09 March 1988 and Friend et al (Friend et al Proc. Natl. Acad. Sci. 84:9059-9063, 1987).

Fung teaches nucleic acids that encode RB mutant proteins wherein amino acids in the region 184-192 were mutated at the 184, 186, 188, 189, and 191. Fung also teaches vectors and host cells expressing said RB mutant proteins. These RB mutants showed growth suppression activity (see column 15, lines 21-25 and table I) in tumor cells. Fung teaches the role of RB in cell growth and that the regulation of the activity of RB is by phosphorylation and that there are 17 potential phosphorylation sites that include amino acids 5, 230, 249, 252, 356,

373 that are part of the n-terminus of RB (see lines 57-67 in column 2, column 3, example 9 in column 15, example 12). Example 12 discloses that the role of phosphorylation of RB can be determined by altering these amino acids. Furthermore, Fung teaches that RB in regions of amino acids 184-192, 245-262, and 873-886 (termed P1, P2 and P3) has homology with p53, another tumor suppressor gene (see table I in column 11) and this homology indicates the importance of these regions to function. Fung further teaches that these regions are located outside the domains known to be important for the suppression functions of these proteins. They further teach that mutation in the conserved amino acids in these regions resulted in proteins that have active conformation (see columns 11 and 12).

Dryja et al teach a DNA that has 99.9% sequence similarity in the sequence regions 121-166-2784, 234-2784, and 292-2784 with the instantly claimed DNA segment whose nucleotide sequence is closed in SEQ ID No 30, 32, and 34 respectively. When translated these regions (166-2784, 234-2784, and 292-2784) would encode amino acid sequences disclosed in SEQ ID No 31, 33, and 35 respectively, except the first methionine (see comparisons with the accession no I05311 disclosed in cited patent).

Friend et al teach a RB DNA that has 99.9% sequence similarity and identity with the sequence disclosed in SEQ ID No 28. This DNA sequence also translated to an amino acid sequence that has 100% amino acid sequence similarity and identity disclosed in SEQ ID NO 29, except for the first amino acid (sequence comparisons of SEQ ID NO 28 and 29 with the accession no M33647 in Friend et al).

It would have been obvious to one of ordinary skill in the art at the time of the claimed invention to modify the make deletions in the N-terminal region of RB using the DNA taught by Dryja or Friend et al, make vectors and study their effect on the growth of transformed cells with a reasonable expectation of success. An artisan would have been motivated to delete parts of the N-terminus of RB sequentially because it has phosphorylation sites that may be relevant to RB function and also because it has regions that, though are not located in the known DNA binding domains, are important for function (as taught by Fung in columns 11 and 12). Regarding the vectors of claims 25 and 26, it is noted that it would have been obvious to make adenoviral vectors or adenovirus comprising the deletion mutants of RB because these

vectors would allow expression of the mutant RB proteins in vivo (see lines 61-67 in column 8 and lines 1-16 in column 9 of Fung).

14. It is noted that the rejection of claims 1-7, 23, 24, and 27-30 under 35 USC 102 (Ewen et al. Cell 73:487-497, 1993 and Antelman et al. Oncogene 15:2855-2866, 1997) have been withdrawn in view of the amendment to claim 1. However, these rejections may be reinstated if these amendments are withdrawn.

Response to Arguments:

Applicant's arguments with respect to rejection of claims 1-7, 13, 20-24, and 27-30 under USC 102 and 103 have been considered but are moot in view of the new ground(s) of rejection.

15. No claim is allowed.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608. The fax phone number for this Group is (703) 308-4242.

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Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the Kay Pinkney whose telephone number is (703) 305-3553.

Scott D. Priest

SCOTT D. PRIEST
PRIMARY EXAMINER

Ram R. Shukla, Ph.D.